L3: Entry 152 of 237 File: USPT May 26, 1998

DOCUMENT-IDENTIFIER: US 5756069 A
TITLE: Amphipathic polychelating compounds and method of use

BSPR:
The invention also features a liposome including a lipid bilayer membrane and a polychelating compound bound to the membrane via the lipid-soluble anchor. This liposome can further include a plurality of ions bound to the chelating agents, and may be modified with a targeting group, e.g., an antibody, bound to the membrane. The liposomes can also be modified with a protective polymer bound to the membrane. Such protective polymers are water-soluble, have a chain length longer than that of the hydrophilic polymeric moiety, and have a molecular weight of from, e.g., 500 to 40,000 daltons. Representative polymers include derivatives of polyethylene glycol (PEG), polypropylene glycol (PPG), polyacrylamide, poly N-vinyl pyrrolidone, polyacrylic acid, polyalcohol, ganglioside, polyamino acid, polysaccharide, polyamidoamine, polyethyleneamine, or a copolymer or block copolymer thereof.

BSPR:
In yet a further embodiment, the invention features a method of imaging a target region in the body of a patient by administering a diagnostically effective amount of liposomes to the patient, the liposomes including lipid bilayer membranes, the polychelating compounds of the invention bound to the membranes, and a plurality of labeling ions linked to the chelating agents on the polychelating compounds, allowing sufficient time for the liposomes to accumulate in the target region, and obtaining an image of the target region by detecting the labeling ions in the region. The liposomes can be modified with protective polymers, and/or targeting groups.

DEPR:
The liposomes or micelles containing the amphipathic polychelating compounds can be further modified to alter the natural targeting of liposomes for the macrophage-monocyte system, e.g., liver, spleen, bone marrow, and lymph nodes. For example, liposomes can be modified with a surface-bound targeting group, such as an antibody, to target a particular organ or tissue within the body. Moreover, the liposomes can be modified to include protective polymers to reduce the normal uptake of the liposomes by the macrophage-monocyte system, to significantly increase the circulation time, or half-life, within the body.

DEPR:
Liposomes, with or without added targeting groups, can also be modified to include large water-binding "protective polymers" that are bound to the lipid bilayer membrane to form a protective surface layer which significantly decreases the uptake of the liposomes by the macrophage-monocyte system, e.g., as described in U.S. Pat. No. 4,920,016, which is incorporated herein by reference. Micelles may be similarly modified.

DEPR:
The enhanced signal of the PEG-Gd-Ls is probably due to increased relaxivity of this preparation while the Dext-Gd-Ls accumulates in lymph nodes due to possible receptor-mediated process. Dextran-enhanced accumulation of particulates and conjugates in the lymphatics has been reported previously by Takakura et al., Cancer Res., 44:2505-10 (1984). These results show that

covering the liposomal surface with a protective polymer such as PEG and dextran increases the target pixel intensity 1.5 to 2 times compared to unmodified liposomes.

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L3: Entry 157 of 237 File: USPT Feb 17, 1998

DOCUMENT-IDENTIFIER: US 5718915 A
TITLE: Antiviral liposome having coupled target-binding moiety and hydrolytic enzyme

ABPL:
Complexes are prepared containing two or more different effector molecules joined to each other by a joining component. At least one of the effector molecules can bind to a target molecule and at least one of the other effector molecules has therapeutic properties. The joining component can be liposomes, proteins and organic polymers including dendrimer polymers, and can be of sufficient length and/or flexibility to permit the therapeutic effector molecule to interact with a target at the same time as the binding molecules. An antiviral liposome is prepared by coupling to a liposome outer surface a hydrolytic enzyme capable of digesting a viral component and a target-binding moiety which may be a polypeptide, glycoprotein or glycoprotein fragment having specificity for viruses such as HIV-1, influenza virus and hepatitis virus. The hydrolytic enzyme may be a glycosidase, phospholipase, lipase, cholesterol esterase, nuclease or protease. A second hydrolytic enzyme and target-binding moiety may also be present, and albumin may be coupled to the liposome surface. Within the liposome may be an internal hydrolytic enzyme capable of digesting a viral component.

BSPR:
The present invention provides several different binding molecule-multienzyme complexes capable of specifically binding to a target of interest. The binding molecule-multienzyme complexes of the invention comprise two or more different effector molecules joined to each other by a joining component, wherein at least one of the effector molecules has the property of binding to a molecular target, i.e. a binding effector molecule, and at least one of the other effector molecules is a therapeutic effector molecule. The joining components for use in the binding molecule-multienzyme complexes of the invention may be of a variety of classes including liposomes, proteins, organic polymers (including dendrimer type polymers). Another aspect of the invention to provide binding molecule-multienzyme complexes in which the joining component is of sufficient length and/or flexibility to permit the therapeutic effector molecules to physically interact with the same target as binding molecule at the same time as binding effector molecule is interacting with the target.

DEPR:
The present invention relates to composition of matter that have the property of specifically binding to selected molecular targets of interest, and directing a therapeutic agent to the binding site. The compounds of the invention are collectively referred to as of the invention comprise two or more different effector molecules joined to each other by a joining component, wherein at least one of the effector molecules is a binding effector molecule and at least one of the effectors is a therapeutic effector. The joining component may be any of a variety of forms including liposome, proteins, organic polymers, and the like.

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L3: Entry 89 of 237 File: USPT Aug 3, 1999

US-PAT-NO: 5932462
DOCUMENT-IDENTIFIER: US 5932462 A

TITLE: Multiarmed, monofunctional, polymer for coupling to molecules and surfaces

DATE-ISSUED: August 3, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Harris; J. Milton	Huntsville	AL	N/A	N/A
Veronese; Francesco Maria	Padua	N/A	N/A	ITX
Caliceti; Paolo	Padua	N/A	N/A	ITX
Schiavon; Oddone	Padua	N/A	N/A	ITX

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Shearwater Polymers, Inc.	Huntsville	AL	N/A	N/A	02

APPL-NO: 8/ 443383
DATE FILED: May 17, 1995

PARENT-CASE:
This application is a continuation-in-part and claims the benefit of the filing date of U.S. Ser. No. 08/371,065, filed Jan. 10, 1995, now abandoned.

INT-CL: [6] C12N 9/96, C12N 11/06, C07K 17/00, A01N 63/00
US-CL-ISSUED: 435/188; 424/94.3, 435/177, 435/180, 435/181, 525/54.1, 514/2, 530/402
US-CL-CURRENT: 435/188; 424/94.3, 435/177, 435/180, 435/181, 514/2, 525/54.1, 530/402
FIELD-OF-SEARCH: 435/174, 435/177, 435/180, 435/181, 435/188, 424/94.3, 514/2, 525/54.1, 530/402

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4179337	December 1979	Davis et al.	435/181
☐	4722906	February 1988	Guire	436/501
☐	5168057	December 1992	Oh et al.	435/174
☐	5438040	August 1995	Ekuiuribe	514/3
☐	5643575	July 1997	Martinez et al.	424/194.1

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0 473 084 A2	0000	EPX	
0 400 472 A3	December 1990	EPX	
0 400 486 A3	December 1990	EPX	
0 632 082 A1	January 1995	EPX	
WO 95/11924	May 1995	WOX	

OTHER PUBLICATIONS

H. Wada et al., Antitumor Enzyme: Polyethylene Glycol-modified Asparaginase, Acad. Sci. 613, pp. 95-108 (Dec., 1990).
I. Fuke et al., "Synthesis of poly(ethylene glycol) derivatives with different branchings and their use for protein modification," Journal of Controlled Release 30 pp. 27-34 (1994).
Agri. Biol. Chem., 52 (8) (1988) pp. 2125-2127, Yamasaki et al: "Novel Polyethylene Glycol Derivatives for Modification of Proteins".
Bioconjugate Chemistry, vol. 06, No. 01, Jan., 1995, Washington, D.C., pp. 62-69, XP002004192, Monfardini C. et al: "A Branched Monomethoxypolyethyleneglycol for Protein Modifications".

ART-UNIT: 161
PRIMARY-EXAMINER: Naff; David M.
ATTY-AGENT-FIRM: Bell Seltzer Intellectual Property Law Group of Alston & Bird LLP

ABSTRACT:

Multi-armed, monofunctional, and hydrolytically stable polymers are described having the structure ##STR1## wherein Z is a moiety that can be activated for attachment to biologically active molecules such as proteins and wherein P and Q represent linkage fragments that join polymer arms poly.sub.a and poly.sub.b, respectively, to central carbon atom, C, by hydrolytically stable linkages in the absence of aromatic rings and ester groups in the linkage fragments. R typically is hydrogen or methyl, but can be a linkage fragment that includes another polymer arm. A specific example is an mPEG disubstituted lysine having the structure ##STR2## where mPEG.sub.a and mPEG.sub.b have the structure CH.sub.3 O--(CH.sub.2 CH.sub.2 O).sub.n CH.sub.2 CH.sub.2 -- wherein n may be the same or different for mPEG.sub.a and mPEG.sub.b and can be from 1 to about 1,150 to provide molecular weights of from about 100 to 100,000. The mPEG disubstituted lysine can be purified from a reaction mixture by chromatography in water, including gel filtration chromatography and ion exchange chromatography because the carboxyl group is ionizable. Impurities are removed, including unreacted mPEG and mPEG monosubstituted lysine, to provide the polymer in pure form. Ion exchange chromatography permits fractionation of a greater amount of polymer per run.

49 Claims, 10 Drawing figures

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L3: Entry 189 of 237 File: USPT Sep 3, 1996

DOCUMENT-IDENTIFIER: US 5552141 A
TITLE: Polymeric immunological adjuvants

BSPR:
In many instances, it may be desirable to have an entity of interest Joined to either the adjuvant, the adjuvant containing polymer or the filler surfactant containing polymer. These additives may be involved in ease of isolation of the polymeric product, e.g. liposome, targeting to a particular cell type or site, binding of the polymer to another polymer, forming complexes with other entities, or the like. Thus, any ligand may be Joined to the polymer, where the ligand may include nucleotides, oligonucleotides, peptides, enzymes, toxins, phosphates, saccharides, phthalocyanines, drugs (monomeric or polymeric), amino acids, chromophores, natural ligands such as biotin, lectins, bifunctional reagents, effector molecules, sugars, antigens, dyes, crown ethers, silanes, steroids, haptens, radioactively labelled moieties, chelating agents or the like.